

### **Remarks**

Claims 1-11 and 61-62 are pending in this application. No claim amendments are made in this paper, and no new matter has been introduced. Applicants respectfully submit that the pending claims are allowable for the following reasons.

On pages 2-4 of the Office Action, and in the Advisory Action, the rejection of claims 1-11 as allegedly obvious over Marx *et al.*, *Proc. Am. Soc. Clin. Oncology* 18: 454a (1999) (“Marx”), in view of Pitot *et al.*, *Journal of Clinical Oncology* 15(8): 2910-2919 (1997) (“Pitot”) and U.S. Patent No. 5,622,959 to Priel *et al.* (“the ‘959 patent”) is maintained. In particular, it is contended that because Marx allegedly discloses an anti-angiogenic effect of thalidomide and Pitot and the ‘959 patent allegedly disclose antitumor activities of CPT-11 and CPT, respectively, the claimed invention is obvious. Applicants respectfully traverse this rejection.

First, Applicants respectfully submit that no *prima facie* case of obviousness can be established by the combination of Marx, Pitot and the ‘959 patent because there would have been no motivation to combine the cited references. See Applicants’ Response filed June 24, 2005, the entirety of which is incorporated herein by reference, pages 5-6.

More important, even assuming, *arguendo*, that a *prima facie* case of obviousness can somehow be established by the cited references, Applicants point out that any presumption of obviousness is rebutted by the unexpected results provided by the claimed invention. This is because, as disclosed in the specification, the claimed invention provides an unexpected synergy between thalidomide and a topoisomerase inhibitor (*e.g.*, irinotecan). The specification discloses that when thalidomide is co-administered with irinotecan to patients with metastatic colorectal cancer, a remarkable absence of gastrointestinal toxicity typically associated with irinotecan is observed. The specification, page 31, line 24 - page 32, line 21. Consequently, Applicants respectfully submit that, in view of the unexpected benefits associated with the claimed invention, the rejection of the claims under 35 U.S.C. § 103 should be withdrawn.

Despite this fact, the Examiner contends that the showing of the unexpected results in the specification is not commensurate with the scope of the pending claims. Advisory Action, page 2. Presumably, the Examiner is contending that the scope of the pending claims should be limited to “irinotecan” and “colorectal

cancer,” instead of “a topoisomerase inhibitor” and “cancer.” However, Applicants respectfully point out that the scope of the pending claims is indeed commensurate with the evidence provided by Applicants.

As well-established, non-obviousness of a genus or claimed range may be supported by data showing unexpected results of a species or narrower range in certain instances. *See, e.g., In re Kollman*, 595 F.2d 48, 56 (C.C.P.A. 1979). In *Kollman*, the court concluded that a claim to a broader range was not obvious in view of a narrower range of data provided by the applicant because “one having ordinary skill in the art may be able to ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value thereof.” *Id.* In addition, once unexpected results are submitted, the Examiner should provide evidence to show that why the submitted data cannot be extended to other claimed species or ranges. *See, e.g., In re Cescon*, 474 F.2d 1331, 1334 (C.C.P.A. 1973) (holding that unexpected results showing a claimed compound’s use in benzene rebuts the presumption of obviousness of the claim that recites the use of the compound in an inert solvent or substrate because “no factual basis appears in the record for expecting the compound to behave differently in other environments.”).

Applicants respectfully submit that the unexpected results provided in this application are sufficient to rebut any presumption of obviousness<sup>1</sup> in connection with the whole scope of the pending claims. As the Examiner recognizes, the specification provides unexpected synergy between thalidomide and irinotecan in metastatic colorectal cancer patients. Those of ordinary skill in the art, based on this showing, would have “reasonably extend[ed] the probative value” of this result to other topoisomerase inhibitors and other types of cancer. *Kollman*, 595 F.2d at 56.

This is because it was known at the time of this invention that various topoisomerase inhibitors can be used for the treatment of cancer. *See, e.g.,* Abstracts of Sugiura *et al.*, *Gan To Kagaku Ryoho*, 19(13): 2140-5 (1992), Chau *et al.*, *Free Radic Biol Med.*, 24(4): 660-70 (1998), and Paz-Ares *et al.*, *Brit. J. Cancer*, 78(10): 1329-36 (1998), all of which were submitted in Applicants’ Response filed June 24, 2005 (disclosing anticancer activity of topoisomerase inhibitors CPT-11, topotecan, IST-622,  $\beta$ -lapachone, and GI-147211).

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<sup>1</sup> Applicants again submit that no *prima facie* case of obviousness has been established by the references cited by the Examiner.

In addition, it was known that irinotecan (and thus other various topoisomerase inhibitors) can be used for the treatment of various types of cancer. *See*, Hecht, *Oncology*, 12(8 Suppl. 6): 72-8 (1998) (“Hecht”), also submitted in Applicants’ Response filed June 24, 2005. (“Irinotecan demonstrates activity against a broad spectrum of malignancies, including carcinomas of the colon, stomach, and lung.”) Furthermore, Hecht also teaches that irinotecan is generally associated with gastrointestinal toxicities, *i.e.*, the adverse effects are not limited to where it is used for the treatment of colorectal cancer. Consequently, Applicants respectfully submit that those of ordinary skill in the art would have had a reasonable basis to believe that the synergistic effects achieved by thalidomide and irinotecan in colorectal cancer patients would be equally achievable by thalidomide and other topoisomerase inhibitors in patients with other types of cancer.

No factual basis as to why the synergistic effects shown with thalidomide and irinotecan cannot be achieved with thalidomide and other topoisomerase inhibitors is provided in the Office Action and the Advisory Action. *See Cescon*, 474 F.2d at 1334. Nor do these office actions provide that the synergistic effects cannot be extended to cancer other than colorectal cancer. *Id.* Therefore, Applicants respectfully submit that the full scope of the claims are non-obvious in view of data presented in the specification. Consequently, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 103 be withdrawn.

### **Conclusion**

For at least the foregoing reasons, Applicants respectfully submit that claims 1-11 are allowable.

No fee is believed due for this submission. However, should any fees be due for this submission or to avoid abandonment of the application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

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